UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,180	02/26/2004	Catherine C. Turkel	17679 (BOT)	9912

7590 09/30/2010

STEPHEN DONOVAN
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
09/30/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,180	TURKEL ET AL.	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/29/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment filed February 4, 2010 has been entered.

Claims 1, 9 and 16 have been amended. Claims 21-28 are canceled. Claims 1-20 and 29 are under examination.

Rejections Withdrawn

2. In view of Applicant's amendment and response the following rejections have been withdrawn:

a) rejection of claims 1-3, 10-17, 19-20 and 29 under 35 U.S.C. 103(a), pages 2-6, paragraph 3.

b) rejection of claims 1-20 and 29 under 35 U.S.C. 103(a), pages 6-9, paragraph 4.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

3. Claims 1-20 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating acute pain medication overuse disorder comprising administering up to 260 units of botulinum toxin to a patient in need of such treatment does not reasonably provide enablement for a method for treating acute pain medication overuse disorder comprising administering about 3000 units of botulinum toxin of any serotype (including serotype A) made by any manufacturer to a patient in need of such treatment.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification provides working examples that disclose a method of treating acute pain medication overuse disorder comprising administering to a patient 105 to 260 total units of BOTOX® (Examples 1-2).

The instant specification has failed to provide enablement for a method of treating an acute pain medication overuse disorder comprising administering about

3000 units to a patient. It should be noted that claim 1 is directed to a method of treating an acute pain medication overuse disorder caused by overuse of acute pain medication, the method comprising the step of local administration of a pure botulinum toxin, wherein the pure botulinum toxin has a molecular weight of about 150 kDa, to a patient with acute pain medication thereby treating the acute pain medication overuse disorder caused by overuse of acute pain medication, wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication. Thus, the instantly claimed invention encompasses *all serotypes of botulinum toxin as well as encompassing botulinum toxin prepared by any manufacture.* The current claims read on administering 3000 units of botulinum toxin A intradermally to a patient. Claims 4, 9 and 18 even recite "3000 units" as the upper-limit of the amount of botulinum toxin that can be given.

The state of the art regarding botulinum toxin administration to subjects (humans) is cited below.

Gil et al *(U.S. Patent No. 6,787,517 published September 7, 2004)* teach that botulinum toxin is the most lethal natural biological agent known to man and has a very potent LD_{50} (column 2). Gil et al teach that a specific dose of a toxin that would be lethal to 50% of the population of a certain species of an animal is called the LD_{50} (column 2). Gil et al teach that the estimated LD_{50} of botulinum toxin A (available from Allergan, Inc., BOTOX®) in humans is about 150,000 picograms or about 3000 units (column 2). Carruthers et al *(U.S. Patent No. 6,358, 917 B1 published March 19, 2002)*

teach that botulinum toxin (BTX) is administered in units (column 3). Carruthers et al teach that "unit equivalents" is an amount of botulinum toxin which is equivalent to standard units of botulinum toxin A (column 3). Carruthers et al teach that a standard unit of BTX-A is defined as the L_{50} for female Swiss Webster mice weighing 18-20 grams (column 3). Carruthers et al teach that the estimated human LD_{50} (for a 70-kg person is 40 units/kg or about 2500-3000 units (column 3).

It should be noted that the claimed dosage range includes all botulinum toxins prepared by any manufacturer. The instant specification has failed to enable the claimed method of treating acute medication overuse disorder by *administering about 3000 units of any botulinum toxin.* Based on the teachings of the cited art the skilled artisan would not administer about 3000 units of for example, BOTOX® (botulinum toxin serotype A) to a patient, (e.g. human patient) to treat an autoimmune disorder since the cited art has taught that the estimated human LD_{50} for a 70-kg person is 40 units/kg or about 2500-3000 units of BOTOX®. The instant specification has failed to enable one of skill in the art to make and use the invention commensurate in scope with these claims.

In view of all of the above, Applicant has not satisfied the requirements as set forth under 35 U.S.C. 112 first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 5 and 8 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 5 and 8 "…depend from claim 1 which recited "a local step of intradermal administration...". Claim 5 recites intramuscular or subcutaneous administration, when independent claim 1 is directs the invention to *intradermal administration*. Claim 8 recites "... to a muscle location from which the patient perceives a pain to arise", when independent claim 1 is directs the invention to intradermal administration. How can the mode of administration for the invention be intradermal and a dependent claim recite intramuscular or subcutaneous administration? It should be noted that intradermal means between the layers of skin and not into a muscle. Correct and/or clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 10-17, 19-20 and 29 are rejected under 35 U.S.C. 103(a) as unpatentable over Schim *(Current Medical Research and Opinion, Vol. 20, No,1,*

January 2001, p. 49-53) in view of Johnson et al *(U.S. Patent No. 5,512, 547 issued April 30, 1996)* in view of *Cephalalgia, An International Journal of Headache*, Volume 24, Supplement 1, 2004 (*Cephalalgia, 2004*) and further in view of Aoki et al *(U.S. Patent No. 6,896,886 B2 filed July 16, 2001, issued May 24, 2005).*

Independent claim 1 is directed to a method of treating an acute pain medication overuse disorder caused by overuse of acute pain medication, the method comprising the step of local administration of a pure botulinum toxin, wherein the pure botulinum toxin has a molecular weight of about 150 kDa, to a patient with acute pain medication thereby treating the acute pain medication overuse disorder caused by overuse of acute pain medication, wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication.

Schim teaches a method of treating medication overuse disorder by administering to a patient botulinum toxin (includes complexing proteins) (page 51). Schim teaches this method because Schim teaches that botulinum toxin was administered to patients with and without analgesic overuse (Study 3, page 51). Schim teaches that botulinum toxin was effective in treating patients with medication overuse disorder (page 51).

Schim do not teach pure botulinum toxin.

Johnson et al teach that pure botulinum toxin (without complexing proteins) has advantages over the botulinum toxin complex because of their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at

temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less (column 4).

Schim and Johnson et al do not specifically teach the claim limitations "wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication".

Cephalalgia teaches that medication-overuse is an interaction between a therapeutic agent and used excessively and susceptible patient (page 94). *Cephalalgia* teaches that the best example is overuse of symptomatic headache drugs causing headache in the headache-prone patient (page 94). (*Cephalalgia, 2004*), which teaches that the most common migraine-like headache occurs on ≥ 15 days per month and occur as a mixture of migraine-like and tension-like headaches (page 94). *Cephalalgia, 2004* teach that these patients overuse migraine drugs and /or analgesics (page 94). *Cephalalgia, 2004* teach that diagnostic criterion used for these patients is ≥ 10 days per month of drug use, this translates into 2-3 treatment days a week (page 94). Based on the definition given by *Cephalalgia*, the claim limitations "wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication" are necessarily taught in the art because Schim teaches the treatment of "medication overuse patients".

Schim, Johnson et al and Cephalalgia do not specifically teach intradermal administration.

Aoki et al teach that botulinum toxin can be used to treat various disorders including headaches and conditions associated with pain (see the Abstract and column 10, Example 11). Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration (column 10, claim 3).

It would be prima facie obvious at the time the invention was made to substitute the botulinum toxin complex as taught by Schim for the pure botulinum toxin as taught by Johnson et al by intradermal administration as taught by Aoki et al used in a method of treating medication overuse disorder (defined by Cephalalgia) because Johnson et al teach that high specific activity preparations reduce the probability of patients developing neutralizing antibodies and it obviously would be desirable to have higher specific activity preparations than those currently available and Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration. Additionally, Johnson et al teach that the primary advantageous of the compositions of the invention are their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of $0^{o}C$ which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of $-10^{o}C$ or less.

It would be expected, absent evidence to the contrary, that administering intradermally a composition comprising pure botulinum toxin would be effective in

treating medication disorder as well as requiring a lower dosage of botulinum toxin and minimize the development of neutralizing antibodies in these patients.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one method, and a person of ordinary skill would recognize that it would be used in similar methods in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar element according to known methods is likely to be obvious when it does no more than yield predictable results". Thus, the combination of prior art references as combined provided a *prima facie* case of obviousness.

6. Claims 1-20 and 29 are rejected under 35 U.S.C. 103(a) as unpatentable over Tepper et al *(Cephalagia, 2003, 23, 581-762)* in view of Johnson et al *(U.S. Patent No. 5,512, 547 issued April 30, 1996)* in view of *Cephalalgia, An International Journal of Headache*, Volume 24, Supplement 1, 2004 (*Cephalalgia, 2004*) and further in view of Aoki et al *(U.S. Patent No. 6,896,886 B2 filed July 16, 2001, issued May 24, 2005).*

Independent claim 1 is directed to a method of treating an acute pain medication overuse disorder caused by overuse of acute pain medication, the method comprising the step of local administration of a pure botulinum toxin, wherein the pure botulinum toxin has a molecular weight of about 150 kDa, to a patient with acute pain medication thereby treating the acute pain medication overuse disorder caused by overuse of acute pain medication, wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication.

Tepper et al teach a method of treating medication overuse disorder by administering to a patient botulinum toxin (includes complexing proteins) (page 715). Tepper et al teach that the patients were administered 100 units of botulinum toxin A (page 715). Tepper et al teach that botulinum toxin was effective in treating patients with medication overuse disorder (page 715).

Tepper et al do not teach pure botulinum toxin.

Johnson et al teach that pure botulinum toxin (without complexing proteins) has advantages over the botulinum toxin complex because of their high percentage

recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of 0°C which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of -10°C or less (column 4).

Tepper et al and Johnson et al do not specifically teach the claim limitations "wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication".

Cephalalgia teaches that medication-overuse is an interaction between a therapeutic agent and used excessively and susceptible patient (page 94). *Cephalalgia* teaches that the best example is overuse of symptomatic headache drugs causing headache in the headache-prone patient (page 94). (*Cephalalgia, 2004*), which teaches that the most common migraine-like headache occurs on ≥ 15 days per month and occur as a mixture of migraine-like and tension-like headaches (page 94). *Cephalalgia, 2004* teach that these patients overuse migraine drugs and /or analgesics (page 94). *Cephalalgia, 2004* teach that diagnostic criterion used for these patients is ≥ 10 days per month of drug use, this translates into 2-3 treatment days a week (page 94). Based on the definition given by *Cephalalgia*, the claim limitations "wherein the patient takes the medication prior to experiencing pain and experiences pain after the intake of acute pain medication thereby treating the acute pain medication overuse disorder caused by the overuse of acute pain medication" are necessarily taught in the art because Tepper et al teaches the treatment of "medication overuse patients".

Tepper et al, Johnson et al and Cephalalgia do not specifically teach intradermal administration.

Aoki et al teach that botulinum toxin can be used to treat various disorders including headaches and conditions associated with pain (see the Abstract and column 10, Example 11). Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration (column 10, claim 3).

It would be prima facie obvious at the time the invention was made to substitute the botulinum toxin complex as taught by Tepper et al for the pure botulinum toxin as taught by Johnson et al by intradermal administration as taught by Aoki et al used in a method of treating medication overuse disorder (defined by *Cephalalgia*) because Johnson et al teach that high specific activity preparations reduce the probability of patients developing neutralizing antibodies and it obviously would be desirable to have higher specific activity preparations than those currently available and Aoki et al teach that botulinum toxin can be used to treat patients by intradermal administration. Additionally, Johnson et al teach that the primary advantageous of the compositions of the invention are their high percentage recovery of biologically active neurotoxin and their long-term stability (shelf-life) at temperatures of $0^{o}C$ which in contrast to the current commercial available products that have a low percentage recovery of biological active neurotoxin and must be stored at temperatures of $-10^{o}C$ or less. It would be expected, absent evidence to the contrary, that administering intradermally a composition comprising pure botulinum toxin would be effective in treating medication

disorder as well as requiring a lower dosage of botulinum toxin and minimize the development of neutralizing antibodies in these patients.

Status of Claims

7. No claims allowed.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to VANESSA L. FORD whose telephone number is (571)272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571.272.0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Primary Examiner, Art Unit 1645
September 15, 2010